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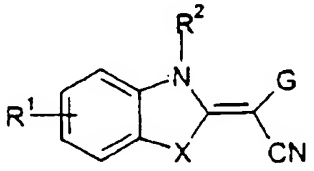
(54) Benzazole derivatives and their use as JNK modulators

(57) The present invention is related to benzazole derivatives according to formula I



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wherein

X is O, S or NR^0;

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

notably for use as pharmaceutically active compounds. Said benzazole derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective inhibitors of JNK2 and/or 3. The present invention is furthermore related to certain novel benzazole derivatives of formula I.

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Formulation 4 - Tablets

[0103] A benzazole compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active benzazole compound) in a tablet press.

Formulation 5 - Injection

[0104] A benzazole compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 6 : Biological assays

[0105] **JNK2 and 3 in vitro assays:** JNK3 and/or 2 assays are performed in 96 well MTT plates, by incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM $^{33}\gamma$-ATP (2 nCi/µl), in the presence or absence of benza-zole inhibitors and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM $MgCl_2$; 1 mM Dithiothreitol, and 100 µM $NaVO_4$. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer. After incubation for 60 minutes at RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above. By substituting GST-c Jun for biotinylated GST-$_1$ATF$_2$ or myelin basic protein, this assay can be used to measure inhibition of preactivated p38 and ERK MAP Kinases, respectively.

[0106] **Sympathetic Neuron Culture and Survival Assay** : Sympathetic neurons from superior cervical ganglia (SCG) of newborn rats (p4) are dissociated in dispase, plated at a density of 10^4 cells/cm^2 in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 µg/ml NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 10^5M. Cell death is induced at day 4 after plating by exposing the culture to medium containing 10 µg/ml of anti NGF anti-body (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of benzazole inhibitors. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/ml of 3-(4,5-dimethylthiazol-2-yl)2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are resuspended in DMSO, transferred to a 96 MTT plate and cell viability is evaluated by measuring optical density at 590 nm.

Biological Results

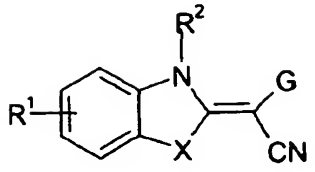
[0107] The activities of the benzazole derivatives claimed in the formula I were assessed using the above described *in vitro* and *in vivo* biologicals assays. Representative values are given in the table shown below:

Compound	*JNK3*	*JNK2*	*p38*	*ERK2*
1	290	500	>30000	>30000
5	400	1200	>30000	>30000
15	70	210	>30000	>30000
20	950	2300	>30000	>30000
28	960	1800	>30000	>30000
40	105	450	>30000	>30000

[0108] The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC_{50} (nM), i.e. the amount necessary to achieve 50% inhibition of said target (e.g. JNK2 or 3). AS# denotes an exemplary test compound as set out with its number in the above examples. From the above table it could be derived that said test compounds according to formula I do have a significant effect both on JNK2 and more notabyl on JNK 3, but virtually no effect onto p38 and ERK2, thus delivering a quite selective inhibitory effect.

Claims

1. Benzazole derivatives according to formula I



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as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

X is O, S or NR^0, with R^0 being H or an unsubstituted or substituted C_1-C_6 alkyl;

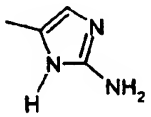
G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

R^1 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted C_1-C_6-thioalkoxy, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

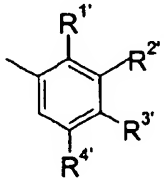
R^2 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^3R^{3'}$, -$(SO_2)R^3$, with

R^3 and $R^{3'}$ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl,

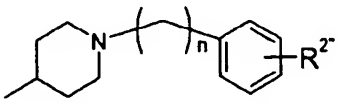
with the proviso that if X is S or NH, while R^1 and R^2 are both H, G shall not be



with the further proviso that if X is S, R^1 and R^2 are both H, G shall not be

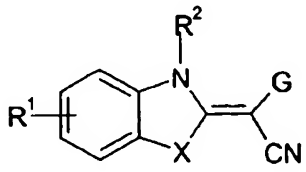


with $R^{1'}$ being H, methyl or —OCH_3; $R^{2'}$ and $R^{3'}$ being H or methyl and $R^{4'}$ being H, methyl or —OCH_3, with the further proviso that if X is S or O, R^1 and R^2 are both H, G shall not be



with $R^{2''}$ being H, lower alkyl, lower alkoxy or halogen and with n = 1-4,
with the final proviso that if X is O, S or NR, with R being H, C_1-C_4 alkyl or aryl, G shall not be a 4-diazo-, or 4-diazoniumphenyl group.

2. Benzazole derivatives according to formula I



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as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

X is O, S or NR^0, with R^0 being H or an unsubstituted or substituted C_1-C_8 alkyl;

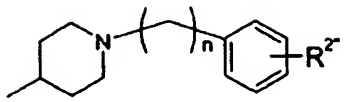
G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

R^1 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted C_1-C_6-thioalkoxy, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

R^2 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^3R^{3'}$, -$(SO_2)R^3$, with

R^3 and $R^{3'}$ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl,

with the proviso that if X is S or O, R^1 and R^2 are both H, G shall not be.



with $R^{2'}$ being H, lower alkyl, lower alkoxy or halogen and with n = 1-4, for use as a medicament.

3. A benzazole derivative according to claim 1 or 2, wherein R^2 is hydrogen, an unsubstituted or substituted C_1-C_6 alkyl, an unsubstituted or substituted C_1-C_6 alkylaryl or C_1-C_6 alkyl-heteroaryl group, -C(O)-R^3, -C(O)-$NR^3R^{3'}$, -$(SO_2)R^3$, whereby R^3 and $R^{3'}$ are as above defined.

4. A benzazole derivative according to any of the preceding claims, wherein R^2 is hydrogen and R^1, X and G are as above defined.

5. A benzazole derivative according to any of the preceding claims, wherein R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy.

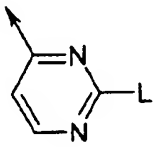
6. A benzazole derivative according to claim 4, wherein R^3 and $R^{3'}$ are selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, C_1-C_6-alkyl aryl, C_1-C_6- alkyl heteroaryl.

7. A benzazole derivative according to claim 6, wherein R^3 and $R^{3'}$ is hydrogen or C_1-C_6 alkyl.

8. A benzazole derivative according any of the preceding claims, wherein said aryl or heteroaryl group is substituted with at least one substituent selected from the group consisting of unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted alkynyl, amino, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6- alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, C_1-C_6 alkoxythio.

9. A benzazole derivative according to any of the preceding claims, wherein G is an unsubstituted or substituted pyrimidinyl group.

10. A benzazole derivative according to claim 9, wherein G is a pyrimidinyl group



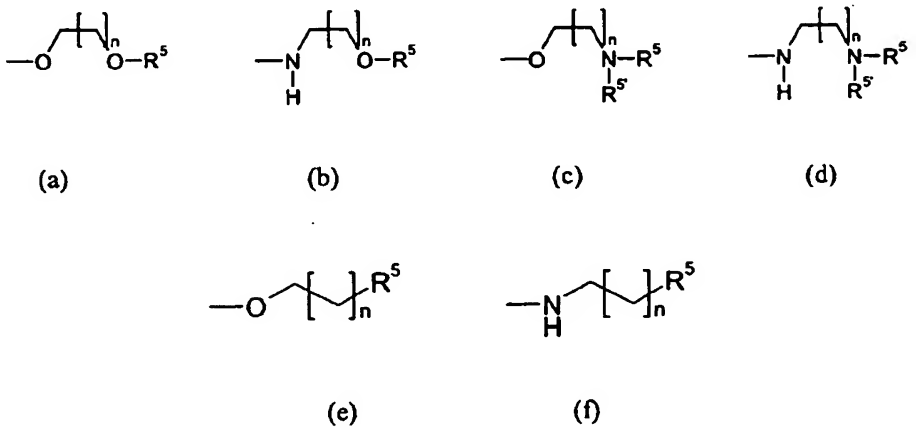
wherein L is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_8 alkoxy, unsubstituted or substituted C_1-C_8 thioalkoxy, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, amino-(C_1-C_{10})alkyl, amino- unsubstituted or substituted (C_1-C_{10})-alkyl-aryl, amino-unsubstituted or substituted (C_1-C_{10})alkylheteroaryl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted 3-8 membered cycloalkyl, optionally containing at least one heteroatom selected from N, O, S, and unsubstituted or substituted hydrazido groups.

11. A benzazole derivative according to claim 10, wherein L is a substituted or unsubstituted (C_1-C_{10})-alkyl group.

12. A benzazole derivative according to claim 10, wherein L is a group -N(R^a, R^b) or -OR^a, with R^a and R^b being each independently selected from the group consisting of H, unsubstituted or substituted (C_1-C_{10})-alkyl, unsubstituted or substituted C_1-C_6 alkyl-aryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, unsubstituted or substituted

aryl or heteroaryl and unsubstituted or substituted 4-8 membered saturated or unsaturated cycloalkyl.

13. A benzazole derivative according to claim 12 wherein L is selected from



(a) (b) (c) (d)

(e) (f)

wherein n is 1 to 10, preferably 1 to 6
R^5 and $R^{5'}$ are independently selected from each other from the group consisting of H, substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted aryl or heteroaryl, substituted or unsubstituted C_1-C_6 alkyl-aryl and substituted or unsubstituted C_1-C_6-alkyl-heteroaryl.

14. A benzazole derivative according to claim 13, wherein $R^{5'}$ is an unsubstituted or substituted imidazolyl.

15. A benzazole derivative according to any of the preceding claims, wherein X is S, R^1 is H and R^2 is H.

16. A benzazole derivative according to any of the preceding claims selected from the following group:

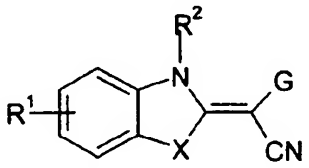
1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)-acetonitrile
1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl[3-chloro-5-(trifluoromethyl)-2-pyridinyl]acetonitrile
1,3-benzothiazol-2-yl(2-chloro-6-methyl-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(6-chloro-5-nitro-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl(2-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl(2-oxo-2,3-dihydro-4-pyridinyl)acetonitri le
1,3-benzothiazol-2-yl(2-phenyl-4-quinazolinyl)acetonitrile
(6-chloro-1,3-benzothiazol-2-yl)(phenyl)acetonitrile
1,3-benzothiazol-2-yl(5-chloro-2-pyridinyl)acetonitrile
1,3-benzothiazol-2-yl(phenyl)acetonitrile
1,3-benzothiazol-2-yl(6-chloro-2-pyridinyl)acetonitrile
1,3-benzothiazol-2-yl(2-pyrazinyl)acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(1H-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-{4-[2-(4-morpholinyl)ethyl]-1-piperazinyl}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl{2-[4-(benzyloxy)-1-pipefidinyl]-4-pyrimidinyl}acetonitrile
1,3-benzothiazol-2-yl[2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-hydrazino-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-(dimethylamino)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl{2-[(2-methoxyethyl)amino]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl{2-[(2-hydroxyethyl)amino]-4-pyrimidinyl}acetonitrile
1,3 -benzothiazol-2-yl[2-(propylamino)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2- {[3-(1H-imidazol-1-yl)propyl]amino}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl[2-(1-pyrrolidinyl)-4-pyrimidinyl] acetonitrile
1,3-benzothiazol-2-yl {2-[(2-phenylethyl)amino]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(2-pyridinyl)ethyl]amino}-4-pyfimidinyl)acetonitrile
1,3-benzothiazol-2-yl{2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl{2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl{2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl}acetonitrile
1,3-benzothiazol-2-yl{2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(3-pyridinyl)ethyl] amino}-4-pyrimidinyl)acetonitrile le
1,3-benzothiazol-2-yl(5-bromo-2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)-acetonitrile
(2-chloro-4-pyrimidinyl)(3-methyl-1,3-benzothiazol-2(3H)-ylidene)ethanenitrile
1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)acetonitrile
1,3 -benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(1H-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl{2-[(2-hydroxyethyl)amino]-4-pyrimidinyl}acetonitrile
1,3 -benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)acetonitrile

17. A benzazole derivative according to claim 16, which is selected from the group consisting of:

1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
1,3-benzothiazol-2-yl(2-{[2-(1H-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)acetonitrile
1,3-benzothiazol-2-yl {2-[(2-hydroxyethyl)amino]-4-pyrimidinyl} acetonitrile
1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)acetonitrile

18. Use of a benzazole derivatives according to formula I



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as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

X is O, S or NR^0, with R^0 being H or an unsubstituted or substituted C_1-C_6 alkyl;

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

R^1 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted C_1-C_6-thioalkoxy, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or sub-

stituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

R^2 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^3R^{3'}$, -$(SO_2)R^3$, with

R^3 and $R^{3'}$ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl,

for the preparation of a pharmaceutical composition for the modulation of the JNK pathway.

19. Use according to claim 18 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK.

20. Use according to claim 19 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK2 and/or 3.

21. Use according to any of claims 19 to 20 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Parkinson's disease, retinal disease, spinal cord injury, head trauma.

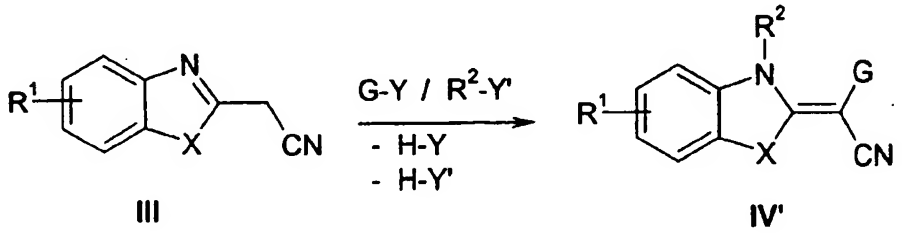
22. Use according to any of claims 19 to 20 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic schock, transplant rejection.

23. Use according to any of claims 19 to 20 for the treatment of cancer including breast-, colorectal, pancreatic cancer.

24. Use according to any of claims 19 to 20 for the treatment of cardiovascular diseases including stroke, arteriosclerosis, myocordial infarction, myocordial reperfusion injury.

25. A pharmaceutical composition containing at least one benzazole derivative according to any of the claims 2 to 17 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

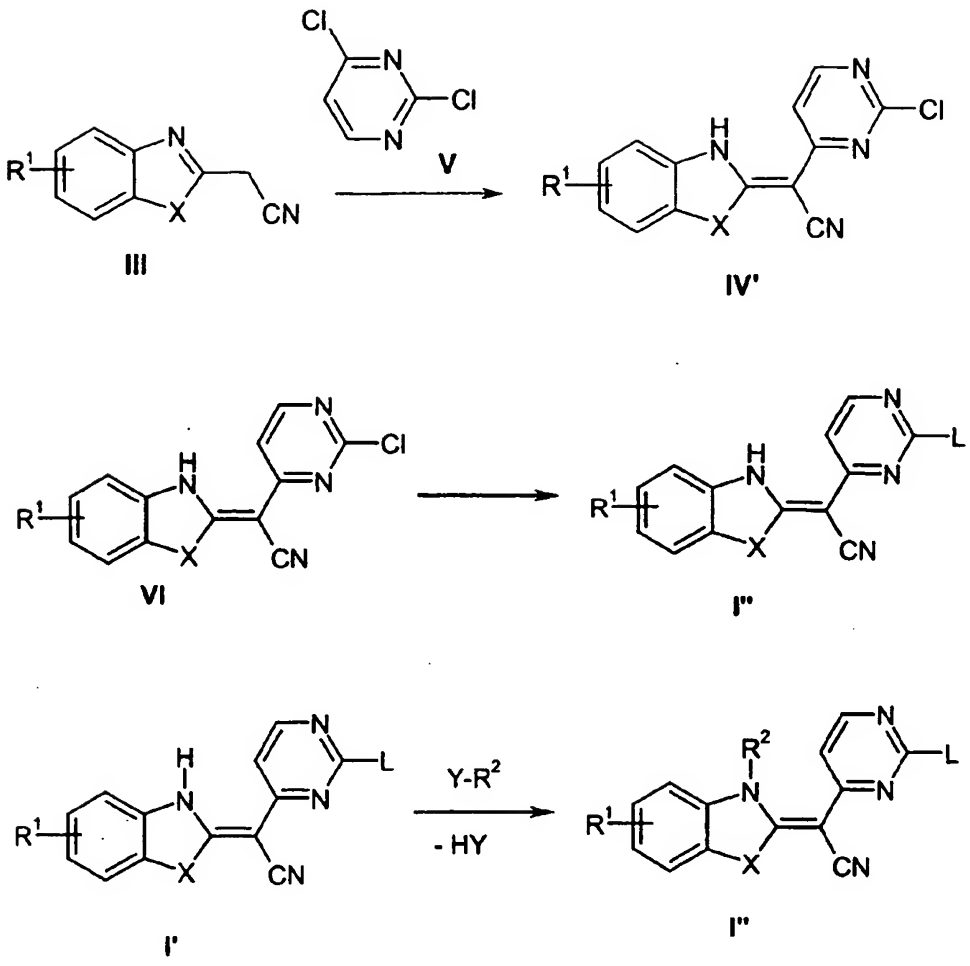
26. Process for the preparation of a benzazole derivative according to any of claims 1 to 17, wherein the following reaction is performed :



III IV'

whereby X and G are as above described and Y, Y' are suitable leaving groups like halogen.

27. Process according to claim 26, wherein the following reactions are performed :



with R^1, R^2, Y and X being as described above.

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